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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/936,377 | 02/26/2002 | Catherine Defrenne | BM45379 | 4141 |

25308 7590 06/15/2004

DECHERT
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| EXAMINER | |
|---|---|
| BASKAR, PADMAVATHI | |
| **ART UNIT** | **PAPER NUMBER** |
| 1645 | |

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/936,377 | DEFRENNE ET AL. | |
| | Examiner | Art Unit | |
| | Padmavathi v Baskar | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *25,27,29,31,32,35,40,41,43 and 47-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,27,29,31,35,40,41,43 and 47-51* is/are rejected.

7)☒ Claim(s) *32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### Amendment

1. Applicant's amendment filed on 4/19/ 04 is acknowledged.

***Status of Claims***

2. Claims 25, 27, 29, 31, 32, 35, 40, 41, 43 and 47-51 are pending in the application.

***35 U.S. C. 112, first paragraph, written description rejection withdrawn***

3. In view of arguments of record, the rejection of claims 25, 27, 29, 31, 35, 40, 41, 43 and 47-51 under 35 U.5.C. 112, first paragraph (written description) is withdrawn.

***Claim Rejection - 35 U.S. C. 112, first paragraph maintained***

4. The rejection of claims 25, 27, 29, 31, 35, 40, 41, 43 and 47-51 under 35 U.5.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising the amino acid sequence SEQ ID NO: 2, a fusion protein comprising the amino acid sequence SEQ.ID.NO: 2, and an immunogenic composition comprising the amino acid sequence SEQ.ID.NO: 2 and a pharmaceutically acceptable carrier does not reasonably provide enablement for a polypeptide comprising a fragment sequence of at least 15 or 20 (the examiner is considering these as fragments) contiguous amino acids of SEQ.ID.NO: 2, where in the immunogenic fragment , when administered to a subject in a suitable composition which can include an adjuvant, or suitable carrier coupled to the polypeptide, induces an antibody or T-cell response that recognizes the polypeptide SEQ.ID.NO: 2 is maintained as set forth in the previous office action.

The claims are drawn to an isolated polypeptide comprising a member selected from the group consisting of (a) the amino acid sequence matching SEQ.ID.NO: 2; (b) an immunogenic fragment comprising at least 15 or 20 (the examiner is considering these as fragments) contiguous amino acids of SEQ.ID.NO: 2, where in the isolated polypeptide, when administered

to a subject in a suitable composition which can include an adjuvant, or suitable carrier coupled to the polypeptide, induces an antibody or T-cell response that recognizes the polypeptide SEQ.ID.NO: 2.

The instant claims are evaluated for scope of enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the disclosed invention is an isolated polypeptide of SEQ ID NO: 2 from *Neisseria mengitidis* ATCC 13090 strain which is designated as a " BASB082" polypeptide in examples 1-5. The specification teaches that this polypeptide has been obtained by recombinant cloning and contains 758 amino acids. However, the specification is silent in disclosing whether this polypeptide recognizes antibodies that are obtained from Neisseria infected individuals. Further, the specification fails to indicate or teach any description of any such fragments that are able to bind to antisera raised against full-length polypeptide and provides no working examples demonstrating (i.e., guidance) enablement for any *fragments and* uses of the claimed polypeptide.

The state of the prior art indicates that protein chemistry is probably one of the most unpredictable areas of biotechnology and is highly complex. As taught by the prior art (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6), the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis. The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67) teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which products proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition.

In addition to the art-recognized unpredictability, the specification has not provided any guidance as to how an artisan would have dealt with the art recognized difficulties related to the unpredictability as raised above. The specification, however, provides no working examples demonstrating enablement for making and using the claimed fragments. Thus, making and using fragments of a polypeptide must be considered highly unpredictable, requiring a specific demonstration. Absent such demonstration, the skilled artisan would be forced into undue experimentation to make and use the invention commensurate in scope with these claims.

Applicants' arguments filed on 4/19/04 have been fully considered but they are not deemed to be persuasive.

Applicant states that the review of wands factors as applied to the present claims supports applicants assertion that the claims are enabled and submitted Exhibits A, B, C and D (reference articles) to support the scope of enablement for the rejected claims.

The examiner has reviewed exhibit A, B, C, and D and specifically noted that Geyson (exhibit D) et al showed that antisera to the whole antigen was used to scan the specific peptide sequences. Thus, the peptides have been shown to bind to antibody raised against the whole antigen. It is noted specifically that the peptides disclosed in screening epitopes consists only peptides and nothing else of that antigen. However, the claimed isolated polypeptide comprises fragments of 15 or 20 contiguous amino acids of SEQ.ID.NO: 2 but also other unknown amino acids and thus bind to any antibody in a non-specific manner. The examiner would like to bring applicant' attention to claim 32, which is not rejected as the isolated polypeptide consists of SEQ.ID.NO: 2.

With respect to T-cell mediated immune response, the specification, however, provides no working examples demonstrating (i.e., guidance) enablement for use of the claimed polypeptides in stimulating and/or expanding T-cells specific for a *Neisserial antigen*. The induction and expansion of specific T-cells to peptide epitopes from protein antigens is highly complex as taught by the prior art, Unanue. ER 1999 (see attached review article, American Journal of Pathology; 154; 651-664). It is apparent that the immunogenicity of T-cell epitopes has been particularly difficult to define because of the added complexity resulting from the need for a first step for processing, and peptide interaction with major histocompatibility molecules (MHC) proteins. Further, protein antigens must be handled by antigen presenting cells (APC) to

be recognized by the T-cells (see page 651, left column, second paragraph through right column). Following a period of internalization by the macrophages, the T-cells were able to recognize products of bacteria. However, chemical neutralization of proteolytic activity abolished the expansion of the T-cell epitopes (see page 652, left column, first paragraph). Thus interaction of T-cells and APC appear to be complex with bacterial antigens or peptides. Therefore, this rejection is maintained.

***Claim Objection***

5. Claim 32 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Remarks***

6. Claims 25, 27, 29, 31, 35, 40, 41, 43 and 47-51 are rejected.

Claim 32 is objected.

***Conclusion***

7. Accordingly, THIS ACTION IS MADE FINAL. see MPEP ' 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

8. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Padma Baskar Ph.D.

5/20/04